

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Joseph ROBERTS, *et al.*

Title: **PROTECTING THERAPEUTIC COMPOSITIONS
FROM HOST-MEDIATED INACTIVATION**

Appl. No.: 09/972,245

Filing Date: 10/09/2001

Examiner: Richard A. Schnizer

Art Unit: 1635

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Natarajan Sethuraman, declare the following:

1. I obtained a Bachelor of Science from Tamil Nadu Agricultural University in Coimbatore, India in 1983, a Masters of Science from Indian Agricultural Research Institute in New Delhi, India in 1985, and a Doctorate Degree in Entomology, Biochemistry, and Molecular Biology from Indian Agricultural Research Institute in New Delhi, India in 1988. I also was a post-doctoral fellow at Duke University in Durham, North Carolina, USA.

2. Following my post-doctoral studies, I worked as Senior Scientist for the University of South Carolina for 11 years, then as Associate Director and Director of Preclinical Studies at GlycoFi Inc and currently as Senior Director and GlycoFi Site Lead at Merck & Co. I have expertise in, among other things, molecular biology and biochemistry, including enzymology.

3. I am a co-inventor of the above-referenced application entitled "PROTECTING THERAPEUTIC COMPOSITIONS FROM HOST-MEDIATED INACTIVATION."

4. I understand that the pending claims of the above-referenced application are rejected on obviousness grounds as follows: (A) claims 1-3, 5-7, 9, 10, 12, 13, 17, 18 and 41-46 over the combination of Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, and Francis *et al.*; (B) claim 4 over the combination of Kawashima, Ettinger, Saito and Francis in further view of Pedersen; (C) claims 8, 11, and 20-22 over the combination of Kawashima, Ettinger, Saito, and Francis in view of Abuchowski; and (D) claim 19 over the combination of Kawashima, Ettinger, Saito, and Francis in view of Bollin.

5. In rejecting the claims on these grounds, I understand the examiner to suggest that various assays of therapeutic outcome constitute suitable means for measuring biological activity of a modified therapeutic agent, as contemplated in the claimed invention. I disagree with this suggestion on factual grounds, which are explicated below and which, in my opinion, would prompt the same conclusion by others in this field.

6. In fact, such measurements of therapeutic benefit are unsuitable for gauging the biological activity of a modified therapeutic agent. Unacceptably high false negatives are engendered when the enzymatic activity of a modified asparaginase is gauged via an assay measuring erythrocytes, lymphoid cells, granulocytes, blast cells, leukemic blasts, hypocellularity of bone marrow, or peripheral blood counts.

7. Such false negatives arise because the assays in question measure points along a physiological pathway that are far removed from the biological activity itself. In this instance we are speaking of asparaginase-catalyzed hydrolysis of asparagine to aspartic acid. Thus, a modified asparaginase could well be effective in catalyzing the asparagine-to-aspartic acid hydrolysis and yet fail to effect a meaningful or even a detectable therapeutic difference, as measured in any of the noted assays, due to an adverse event along the physiological pathway. [For example, leukemia cells could enhance asparagine synthetase activity in response to the asparagine depletion.]

8. In light of this consideration, practitioners in this field would not view an assay measuring erythrocytes, lymphoid cells, granulocytes, blast cells, leukemic blasts, hypocellularity of bone marrow, or peripheral blood counts as suitable for measuring the enzymatic activity of a modified asparaginase.

9. I declare that the statements made herein of my knowledge are true and all statements on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therein.

12/03/10
Date

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